REMARKS

Summary of the invention

The present invention is generally directed to purified antisense molecules of a length of up to 299 bases that are complementary to, hybridize at high stringency to, or have at least 70% identity to human XIAP IRES or a portion thereof. The invention is also directed to cells and vectors containing these molecules, as well as to methods of using the molecules, cells, and vectors.

Status of claims

Claims 45-46, 48-51, 53-58, and 68-103 are pending. Claims 45-46, 48-51, 53-58, and 68 are withdrawn from consideration as being drawn to non-elected subject matter. Claim 70 is objected to due to an informality. Claims 69-103 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 69-73, 77-88 and 99-103 stand rejected under 35 U.S.C. § 112, first paragraph, for inadequate written description. Claims 99-103 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 69-83 and 86-98 stand rejected under 35 U.S.C. § 102(e) for anticipation. Claims 69-98 stand rejected for nonstatutory obviousness-type double patenting. Applicants address each of these objections and rejections below.

Support for claim amendments

Support for the claim amendments is found throughout the specification and, in particular, at page 12, line 26, to page 13, line 7; page 17, lines 20-22; page 30, line 19; page 31, lines 6-9; and SEQ ID NO: 2. No new matter has been added.

Priority

The Office notes that Applicants have not filed a certified copy of priority document PCT/IB99/01415. Applicants will submit a certified copy of this document

under separate cover in compliance with 35 U.S.C. § 119(b).

The Office further states that there is no reference in the application to priority documents U.S. Application No. 09/121,979, now U.S. Patent No. 6,159,709 ("the '709 patent"), and U.S. Application No. 09/332,319, now U.S. Patent No. 6,171,821 ("the '821 patent"). In response, Applicants direct the Office's attention to the preliminary amendment filed on April 19, 2001, in which references to these priority documents were inserted into the specification. Applicants submit that this preliminary amendment adequately addresses the issues raised by the Office regarding the priority claims.

Information Disclosure Statement

The Office has not considered numerous references submitted with the Information Disclosure Statement filed on April 19, 2001. The April 19, 2001 Information Disclosure Statement states that, under 35 U.S.C. 120, the application relies on prior filings, and that references that were already submitted in those prior applications need not be provided again. Notwithstanding this, Applicants have enclosed a Supplementary Information Disclosure Statement containing copies of the references not considered by the Office as well as additional references.

Specification

The Office objects to the disclosure because it contains an embedded hyperlink. In addition, the Office objects to the occurrence of the phrase "What is claimed is:". These objections are overcome by amendment and can be withdrawn.

Applicants have also corrected an error in the specification, in which SEQ ID NO: 7 is described as spanning positions -153 to -139 in reference to the start codon of the human XIAP IRES DNA sequence (SEQ ID NO: 2). Applicants have identified that SEQ ID NO: 7 in fact spans positions -154 to -140 of SEQ ID NO: 2, and the specification has been amended accordingly. No new matter has been added by these amendments.

Claim Objection

The Office objects to claim 70 due to the lack of a period at the end of the claim. This objection is overcome by amendment and can be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 69-103 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Office, "the claims could be interpreted to either contain an antisense molecule with the requisite region of complementary sequences or that in addition to the complementary region there occur additional sequences. Applicants have amended claim 69 and 86 to clarify that the claimed antisense molecules are of a length of up to 299 bases and either include a base sequence complementary to at least 10 consecutive nucleotides of SEQ ID NO: 2 (claim 69) or hybridize to SEQ ID NO: 2 (claim 86). In view of this amendment, it is clear that the claimed antisense molecules can include additional bases, and this rejection may now be withdrawn.

Claims 71-73 further stand rejected because, according to the Office, "the claims are drawn to conflicting minimum thresholds for complementary sequences," compared to claim 69 (from which claims 71-73 depend). The Office's assertion that there is a conflict between the independent and dependent claims is incorrect. The dependent claims are narrower than the independent claim, as would be expected, but they do not conflict. For example, claim 71 as amended recites that the antisense molecule include a base sequence complementary to at least 14 consecutive nucleotides. This claim depends from claim 69, which recites that the antisense molecule include a base sequence complementary to at least 10 consecutive nucleotides. It will always be true that an antisense molecule that includes a base sequence complementary to at least 14 consecutive nucleotides will also have a base sequence complementary to at least 10 consecutive nucleotides. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Written description

Claims 69-73, 77-88, and 99-103 are rejected under 35 U.S.C. § 112, first paragraph, as being supported by an inadequate written description. The Office contends that while the specification discloses two XIAP IRES sequences (human and mouse XIAP IRES), "the claims read on a broad genus of antisense DNA or RNA molecules targeting transcription or translation of XIAP IRES from any source (not just mice or men)." While not assenting to the Office's position that the claims are not adequately supported by the specification, Applicants meet this rejection by the present claim amendments. As amended, each of the claims now requires that the antisense molecules are of a length of up to 299 bases and either include a base sequence complementary to at least 10 consecutive nucleotides of SEQ ID NO: 2 (claim 69) or hybridize to SEQ ID NO: 2 (claim 86). Additionally, each of remaining rejected claims either depends from claim 69 or claim 86, or refers to claim 69 or 86. Thus, the amendments to claims 69 and 86 address the concerns raised by the Office, and this rejection may now be withdrawn.

Enablement

Claims 99-103 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office lists several factors for consideration in determining whether undue experimentation would be required, including scope or breadth of the claims, nature of the invention, state and unpredictability of the art, amount of guidance provided, number of working examples, and amount of experimentation required.

In order to address the Office's concern regarding the scope or breadth of the claims, Applicants note that the claims, as presently amended, are restricted to a portion of the human XIAP IRES DNA sequence (SEQ ID NO: 2), or subdomains thereof. These claims are thus significantly narrowed, which in turn would substantially reduce the

amount of experimentation required by one skilled in the art to make and/or use the invention.

To provide further enabling support for the presently amended claims, Applicants direct the Office's attention to U.S. Application No. 10/400,382 ("the '382 application"), filed on March 27, 2003 and published as U.S. Publication No. 2003-0190659 on October 9, 2003. The '382 application discloses numerous 19-nucleotide sequences with which the human XIAP IRES DNA sequence possesses 100% sequence identity over 19 nucleotides. In particular, SEQ ID NOS: 13-22 of the '382 application (also referred to in that application as E2, F2, G2, H2, A3, B3, C3, D3, E3, and F3, respectively) each possess 100% sequence identity with 19-nucleotide portions of SEQ ID NO: 2 of the present invention, and thus each falls within the scope of presently amended claims 69 and 86. Collectively, these 19-nucleotide sequences span the region from -260 to +2 relative to the human XIAP start codon.

Table 1 of the '382 application (page 11 of the published application) presents *in vitro* data for numerous nucleobase oligomers, including E2, F2, G2, H2, A3, B3, C3, D3, E3, and F3. Each of these oligomers is shown to mediate down-regulation of XIAP mRNA in H460 lung carcinoma cells and/or T24 bladder carcinoma cells *in vitro*. Of these oligomers, E2, E3, and F3 additionally mediate significant down-regulation of XIAP protein in T24 bladder carcinoma cells. The '382 application notes at page 19, right column, that E2, E3, and F3, among others, show "a consistent ability to decrease XIAP protein or RNA levels by more than 50%." Table 4 of the '382 application (page 19, right column) presents additional data showing the ability of the tested oligomers to downregulate XIAP mRNA in H460 cells at 9 hours post-transfection. Of the above-described oligomers, E2, F2, G2, H2, A3, B3, C3, D3, and E3 are shown to downregulate XIAP mRNA significantly. Taken together, the data presented in the '382 application definitively show that the oligomers described therein inhibit transcription or translation using an *in vitro* assay.

The '382 application further describes *in vivo* experiments demonstrating the efficacy of particular oligomers in a mouse tumor model system. For example, Working Example 10 (page 21, right column) describes the injection of oligomers F3, C5, and G4 into the tumors of mice carrying sub-cutaneous H460 human lung carcinoma xenografts. The '382 specification states: "Two weeks after the last treatment (day 35) tumor volumes of mice treated with F3, C5 or G4 AS oligonucleotides were 70%, 60%, and 45%, respectively, smaller than vehicle controls (Fig. 16)." (page 22, left column). Table 1 of the '382 application, discussed above, shows that these three oligomers all possess the ability to downregulate XIAP protein or RNA levels to a significant extent *in vitro*. Thus, the '382 application provides both *in vitro* and *in vivo* evidence of the efficacy of oligomers F3, C5 and G4 in inhibiting transcription and translation of XIAP and in reducing tumor growth in an animal model.

The Office asserts (page 13 of the Office Action) that it is inappropriate to extrapolate from *in vitro* studies to draw conclusions regarding the likely outcomes of corresponding *in vivo* pharmacokinetic behavior. The Office notes that this may be for a variety of reasons, including delivery and internalization of the molecule being tested. The Office relies on this principle – that *in vitro* evidence does not always imply *in vivo* efficacy – as a basis of rejection of the instant claims. However, Applicants note that the '382 application demonstrates <u>both</u> *in vitro* and *in vivo* data demonstrating the efficacy of numerous oligomers within the scope of the presently amended claims. Thus, while one may not have been certain of the therapeutic efficacy of these oligomers in the complete absence of *in vivo* information, the data of the '382 application show that the tested oligomers are in fact effective in an animal model.

Based on this information, it is reasonable to assert that other, similar oligomers consisting of portions from the human XIAP IRES, for which *in vitro* data exist showing an inhibition of transcription or translation, are likely to have *in vivo* efficacy as well. Because oligos such as F3, C5 and G4 were shown in the '382 application to be effective

in vivo and therefore not to be subject to delivery or internalization problems, it is credible that other XIAP IRES oligomers, when utilized as described in Example 10 of the '382 application, would also not be subject to these problems or limitations.

Applicants note that if the Office doubts the accuracy of any of the statements made in the instant application or in the '382 application, the Office is required to provide support for this belief. Applicants direct the Office's attention to M.P.E.P. § 2164.04, which quotes the court in stating:

> "'[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.'"

For all of the above reasons, the enablement requirement has been satisfied, and the enablement rejection of claims 99-103 should be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 69-83 and 86-98 are rejected as being anticipated under 35 USC § 102(e) by one or more of U.S. Patent No. 6,107,041 ("the '041 patent"), U.S. Patent No. 6,133,437 ("the '437 patent"), U.S. Patent Publication No. 2004-0010136 ("the '136 application"), U.S. Patent Publication No. 2002-0120121 ("the '121 application"), U.S. Patent No. 6,537,751 ("the '751 patent"), U.S. Patent Publication No. 2002-0187946 ("the '946 application"), U.S. Patent No. 6,348,328 ("the '328 patent"), and U.S. Patent No. 6,300,492 ("the '492 patent"). Applicants address these rejections as they apply to the amended 69-83 and 86-98.

As an initial matter, Applicants note that the application that gave rise to '751 patent was filed October 29, 1999, i.e., after applicants priority date of July 24, 1998. The '751 patent does claim priority to a U.S. provisional application filed prior to July 24,

1998. However, the 35 U.S.C. § 102(e) critical reference date of a U.S. patent based on a provisional application is the filing date of the provisional application only if the provisional application(s) properly supports the subject matter relied upon to make the rejection (M.P.E.P. 2136.03). In the present case, the subject matter relied upon by the Office (recitation of SEQ ID NO: 2928) is not found in the provisional application that predates Applicants' July 24, 1998 priority date. Thus, the '751 patent cannot be used to reject the claims under 35 USC § 102(e).

Applicants do not assent to the Office's position that the remaining patents and publications are prior art under 35 USC § 102(e). Nor do Applicants assent to the Office's conclusion that the cited references disclose antisense molecules satisfying the claims as examined. Rather, as is discussed in more detail below, applicants submit that the amended claims are not anticipated by any of the cited art, should they qualify as prior art under 35 USC § 102(e). Applicants reserve the right to contest the status of any of the cited patents and publications as prior art under 35 USC § 102(e) and to pursue the broader claims at a later date.

Applicants now turn to the amended claims. Claims 69 and 86, the two independent claims rejected as lacking novelty over the cited art, have each been amended to limit the claimed antisense molecule to those having a length of no more than 299 bases. None of the '041 patent, the '437 patent, the '136 application, the '121 application, the '946 application, the '328 patent, or the '492 patent discloses such a molecule that also either includes a base sequence complementary to at least 10 consecutive nucleotides of SEQ ID NO: 2 (claim 69) or hybridizes to SEQ ID NO: 2 under high stringency (claim 86), as is required by the claims. On this basis, the rejection of independent claims 69 and 86, as well as dependent claims 70-83 and 87 to 98, as lacking novelty over these references, may now be withdrawn, and such action is respectfully requested.

Double-Patenting Rejections

Claims 69-98 stand rejected for nonstatutory obviousness-type double patenting over claims 8 and 9 of the '709 patent and claim 24 of the '821 patent. Applicants respectfully request that the obviousness-type double patenting rejections be temporarily held in abeyance. If necessary, a terminal disclaimer will be filed at such time as otherwise-allowable subject matter is identified.

New Claims 104-133

Applicants direct the Office's attention to new claims 104-133. It is Applicants' position that these claims are patentable for the all of the reasons provided for claims 69-103, above. In particular, regarding new claim 104, Applicants note that this claim similarly limits the claimed antisense molecules to those having a length of no more than 299 bases, and further require that the claimed antisense molecules have at least 70% sequence identity to SEQ ID NO: 2. Accordingly, for the reasons provided above, this claim is novel over the cited art, as are the claims which depend from or otherwise refer to claim 104.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is respectfully requested. Enclosed is a petition to extend the period for replying for three months, to and including June 3, 2005. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: June 3 2005

Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045